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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,139	12/29/2000	Stephen Quirk	11301-0200 (44039-227522)	1818

21186 7590 06/06/2005

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/753,139	QUIRK ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *4-6,8 -14, 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,15-19 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/0502, 01/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *allowable subject matter*.

The Amendment and Response filed Nov. 12, 2004 is acknowledged. Claim 6 and 22 were amended. Claims 1-23 are pending; claims 1-3, 7, 15-19 and 23 reading on the elected invention and species are the subject of this Office Action.

Detailed Office Action

1. Restriction/election

In their REMARKS Applicants Requested clarification and reconsideration of the restriction requirement (page 7, line 1; page 9, line 5 and page 10 line 5). The examiner, in the Office Action of June 30, 2004, required restriction between two Groups, as well as election of species. Applicant's elected Group 1, related to an MMP regulator comprising a zinc chelator and a TIMP-derived peptide and its composition, and species consisting of AFTA linked to SEQ ID NO: 8 in the reply filed on July 22, 2004.

The examiner in her Office Action of August 5, 2004 inadvertently stated that claims 1-3, 7, 15-19 and 22-23 are under examination. After reconsideration of the claims, previous Office Action and Applicants REMARKS the examiner concludes that original claims 1-3, 7, 15-19, and 23 read on elected invention and species. Thus, **claims 1- 3, 7, 15-19 and 23 are the subject of this Office Action, and further prosecution**. Claims 8-14 remain withdrawn from consideration as drawn to the nonelected invention; claims 4-6, 20, 21 and 22 are withdrawn from consideration as directed to nonelected species; see 37 CFR 1.141(b), however, as indicated in the previous Office Action in the case the product is allowable, pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims directed to the process of using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are the subject to being rejoined and fully examined for patentability under 37 CFR 1.104.

2. Objections

2.1. Specification

Objection withdrawal

Objection to the typographic error on page 8, line 12 is withdrawn.

Objection to the specification for use of the term "chelator" is withdrawn, because Applicants' arguments are found persuasive.

Please correct typographical errors on page 1, the last line, after "and"; page 7, line 14, "administered"; page 8 line 12 after "MMP". As the specification has not been checked to the extent necessary to determine the presence of all possible minor errors, Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

2.2. Claims

Objections withdrawal

Objections to the claims for use of the term "chelator" are withdrawn, because Applicants arguments are found persuasive.

Objection to claims 6 and 22 for reciting the nonexistent SEQ ID NO:11 is withdrawn, because a proper amendment has been entered.

Objection to claims 2 and 18 as being in improper Markush group is withdrawn because Applicants' arguments are found persuasive.

Objections not withdrawn

Please expand all abbreviation recited in the claims for the first time. The argument that "one must read and analyze the claims in light of the specification" or that the abbreviated claim terms "are so well known in the art as not to require description, e.g., EDTA", (REMARKS, page 7, line 20 and further) is not persuasive. Not all abbreviations used in the claims are so commonly known as EDTA, and furthermore only IDA, PSDE and AFTA are expanded in the specification. Applicants themselves admit

that some chelator molecules, e.g. AFTA, "are not according to scientific literature, generally known or used as metal chelators", page 22, last paragraph.

3. Rejections

3.1. 35 USC section 112, second paragraph

Rejection of claims 1-3, 7, 15-19 and 23 for the confusing use of the term MMP regulator is withdrawn in the light of Applicants' arguments.

3.2. 35 USC section 112, first paragraph

3.2.1. Lack of written description

Claims 1-3, 7, 15-19 and 23 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The reasons were explained in the Office Action of August 5, 2004, and are repeated herein for the purpose of discussion.

A. The claims are directed to inhibitors of any matrix metalloprotease, wherein the enzyme is from any natural and man-made source. The claims are missing the description of the matrix protease to be inhibited by the claimed inhibitors. The genus of matrix proteases is a large genus and it is unlikely that all matrix metalloproteases share their inhibitors.

Traversing this rejection Applicants notice,

"Applicants' invention is directed to regulators of MMPs, not to the MMP themselves. Applicants have described at page 2 of the specification the relatively small number of members of the MMP family that have been isolated and characterized, as well as other potential members of the family. One would understand that Applicants intend their invention to regulate those known MMPs and those yet to be isolated and characterized [emphasis added]", page 10, second paragraph of the REMARKS.

Applicants' argument has been fully considered but is found not persuasive. MMP inhibitor has chemical feature determined by the structure of particular MMP it inhibits. In the case of inhibitors claimed their characteristic features are embedded in the structure of the polypeptide "derived from TIMP". What is more important, Applicants themselves emphasize the specificity of MMPs inhibitors:

> "TIMPs form very specific regulatory complexes with MMP's, only regulating a specific subset of the MMPs. **No naturally occurring TIMP molecule singly regulates all types of MMPs** [emphasis added]", page 2 of the specification, second paragraph; and on page 14, line 13, "In a preferred embodiment, the present invention comprises three peptides derived from TIMP regions that have a large number of specific side chain interactions with MMPs. **The exact sequence of the peptide employed allows targeting of specific MMPs** [emphasis added]."

This description, however, does not define the particular MMPs that can be used with particular members of SEQ ID NO: 1 family, SEQ ID NO: 2 family or SEQ ID NO: 3 family presented in Table 1.

The specification teaches that human MMP-9 is inhibited by the inhibitors called ChePep-1, ChePep-2, ChePep-3 ChePep-4, ChePep-5, ChePep-6 whose structure is presented in Table 2. The specification, however, is silent as to what other MMPs are inhibited by these constructs. In their computer assisted modeling of the structure of polypeptides used for construction of inhibitors Applicants applied three dimensional structure of MMP-1, MMP-2, MMP-8 and MMp-9 and TIMP-2/MT-1 or TIMP-1 complexes known in the art; page 28, line 17. Thus, one skilled in the art may expect that the obtained polypeptides of SEQ ID NO: 4-8 will interact with these very MMPs. It is, however, unclear how SEQ ID NO: 1-3 were obtained and how they are related to SEQ ID NO: 4-8. In any event, the specification provides support for inhibiting MMP-9 by elected species, i.e, inhibitor comprising polypeptides of SEQ ID NO: 8 and AFTA.

Regarding "relatively small number of members of the MMP family" Applicants themselves provide in the Information Disclosure Statement of March 5, 2002 a review article by Whittaker and Ayscough (Matrix Metalloproteases and their Inhibitors-Current Status and Future Challenges, Celltransfromations Vol. 17, No. 1, pp. 3-14; no year quoted; please correct Form 1449), which lists 26 MMPs. 26 enzymes of human origin is not a few. In addition, the scope of the claim covers any MMP, from any animal, and/or any man-made enzyme variation.

In their REMARKS Applicants request the right to inhibit all "known MMPs and those yet to be isolated and characterized". Thus, Applicants request the right to the invention, which certainly has not been described at the time of filling, for that reason the claims are rejected.

B. In addition, the base claims 1 and 15 are directed to extremely large genus MMP inhibitors comprising a versatile genus of zinc chelators (zinc binding compounds) and a genus of TIMP-derived peptides. However, the structure of claimed regulators is not sufficiently described in claims and specification.

Providing several members of zinc chelating or zinc binding compounds, (See column A in the request fro restriction requirement.), does not allow for identifying the whole genus of zinc chelators comprising chemicals of versatile structures, not all of them will be suitable for the structure of every MMP, as claimed. Thus, a zinc-binding compound used for construction of inhibitor should be identified by its structure. Secondly, the genus of TIMP derived polypeptides is a large a versatile genus for which Applicant have not provided definition. There are several TIMPs in animal bodies (TIMP-1, - 2, –3, -4) that are about 200 amino acid long. The term "polypeptide" means in the art a chemical compound consisting of less than 100 amino acid residues. Thus, from each TIMP (natural or man-made) one skilled in the art can select thousands of polypeptides that contain 100 or less amino acid residues. In addition, Applicants do not define what they understand by the term TIMP derived polypeptide. Nowhere in the specification Applicants state which residues of TIMP are considered to form "TIMP derived

polypeptide". The elected SEQ ID NO: 8 consists of amino acids 24-28 of human, rabbit, baboon and sheep TIMP-1 and chicken TIMP-3. But this pentapeptde is also a part of fruit fly 95 protein (amino acids 241-245), sea urchin's fibropellin (amino acids 542-546) and of macaque's versican (amino acids 742-746), to mention only a few. Thus, the description "TIMP derived' in not necessary proper for SEQ ID NO: 8. Using sequence indentification numbers for artificial polypeptides disclosed by Applicants provides the proper written description.

Thirdly, Applicants themselves define SEQ ID NO: 1-3, as fragments of TIMP "spanning" certain amino acid residues of MMP (see page 14, line 21 and further, and Table 1). However, they even do not disclose the amino acid sequence of said MMP. Taking into account that there are many matrix metalloproteases, the description "SEQ ID NO: 2 spans MMP amino acids 62-73" and similar description on page 14 are not sufficient.

In summary, the genus of claimed MMP inhibitors comprises thousands of chemical compounds whereas Applicants teach only a few such compounds, i. e., ChePep-1, ChePep-2, ChePep-3 ChePep-4, ChePep-5, ChePep-6 (the elected species) and PSDE covalently linked to SEQ ID NO: 2. Providing one skilled in the art with these representatives of the claimed genus is not sufficient for identifying structural characteristics of the whole genus. Thus claims 1 and 15 are rejected.

Claims 2-3, 7, 15-19 and 23 are included in this rejection because the MMP is not described, as well as zinc chelator is not described, and/or TIMP derived peptide is not described.

Applicants attention is turned to the fact that although claim 2-3, 7, 18-19 and 23 are directed to inhibitors that contain as the zinc chelator AFTA, i.e., the elected species nevertheless, the peptide parts of said inhibitors consists of a genus of thousands of peptides for which the sufficient structural description is lacking in the claims and in the specification.

In view of lack of structural description of claimed inhibitors of MMP, or their compositions, Applicants failed to sufficiently describe the claimed invention in such full,

clear, concise, and exact terms that a skilled artisan would recognize they were in possession of the claimed invention.

3.2.2. Scope of enablement

Claims 1- 3, 7 and 15-23 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons explained in the previous Office Action and repeated herein. They are rejected because the specification, while being enabling for the elected species called ChePep-6, as well as other inhibitors designated ChePep-1 ChePep-2 ChePep-3 ChePep-4 ChePep-5 and PSDE covalently linked to SEQ ID NO: 2, does not reasonably provide enablement for

1) any inhibitor of any MMP that consists of a zinc chelator and a TIMP derived peptide (claim 1 and 15) peptide derived from TIMP that contains at least one cysteine residue (claim7 and 23); and
2) any inhibitor of any MMP that consists of AFTA and a TIMP derived peptide (claims 2-3, 7, 18-19 and 23).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the extremely large number of inhibitors of MMP covered by subgenera (1) - (3). See also the above rejection for lack of written description.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative

skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any inhibitor of any MMP, natural or man-made, wherein said inhibitor consists of:

1) any zinc chelator and any TIMP derived peptide or any peptide derived from TIMP that contains at least one cysteine residue; and

2) AFTA and any TIMP derived peptide.

While methods of chemical synthesis and screening for enzyme inhibitors are well known in the relevant art, and skills of the artisans highly developed, preparing inhibitors of any MMP as described under (1)-(2) above is outside the realm of routine experimentation and has a low probability of success. While enablement is not precluded by the necessity for routine manipulation of chemical structure and screening of synthesized chemicals for required function of inhibitors, if a large amount synthesis and screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that the claimed species have the functionality of inhibitors of MMP. The provision of ChePep-6, consisting of AFTA and SEQ ID NO: 8 and being and effecting inhibitor of MMP-9, as well as several other inhibitors of MMP-9 fails to provide such guidance of inhibitors with major structural variations therefrom which remain encompassed within the scope of the rejected claims.

Without a further guidance on the part of Applicants with regards to the name of MMP to be inhibited and the structure of the claimed inhibitors experimentation left to those in the art is improperly extensive and undue.

Traversing this rejection, Applicants write,

1. "Applicants intended their invention to regulate those known MMPs and those yet to be isolated and characterized with MMP regulators comprising TIMP-derived peptides from TIMPs known at or before filing and subsequent thereto", page 13, line 8.

Furthermore, in the third paragraph on page 13 Applicants assert,

2. "**Once he structure of the MMP is known, the exact sequence of the TIMP-derived peptide can be discerned from a visualization program** [emphasis added."

The arguments are not persuasive, because in the first quotation, Applicants request the right to an inhibitor inhibiting any known (but without reciting the amino acid sequence) and to be discovered MMP (i.e. having unknown amino acid sequence), and in the second quotation they state that the structure of MMP is a prerequisite for modeling the TIMP derived polypeptide. Apart the fact that both arguments are inconsistent, Applicants themselves realize that it is not possible to make and use the claimed invention without knowing the MMP structure. Thus, without structural identification of the MMP the claimed invention is not enabled.

In addition, Applicants assure,

3."Only a relatively small number of members of the MMP family have been isolated and characterized. Only a small number of TIMPs are known. TIMPs I-IV are specific known proteins with known structure. Therefore contrary to the Examiner's assertion, the number of MMP regulators is not extremely large", page 13, line 10.

This argument of Applicants is not persuasive for the following reasons. Firstly, as to the number of the MMPs, at the time the application was filed at least 26 MMPs were known; see the above rejection for lack of written description, and Applicants claim an inhibitor of all known and to be discovered MMPs from all animals and man-made, i.e., the number of MMPs that is enormous. Secondly, the amino acid structure of TIMP is prerequisite for computer modeling of the TIMP derived peptide and although TIMPs I-IV are known for *Homo sapiens* and some other animal species, the structure o all TIMP, from all animals and potentially man-made is not known. Thus, modeling the TIMP derived peptide is not enabled without knowing the structure of TIMP.

Finally,

> "Applicants are not aware of any unpredictability in the art with respect to zinc chelators. One would understand from the disclosure that any zinc chelator would function in Applicants' invention. If the Examiner disagrees, she has the burden of producing documentation showing otherwise", page 13, third paragraph.

This argument of Applicants is not persuasive. Applicants themselves provide evidence that not every chelator will couple to the TIMP derived peptides without chemical modifications; see page 12 of the specification and Fig.8. After the modification a new compound may be still a chelator, but it is not necessary a chelator know in the art. Providing the example how to modify EDTA molecule, which does not form a covalent bond with a peptide, so that it becomes PSDE, which does, is not enabling for modifications of any chelator.

4. Conclusion

Claims 1-3, 7 and 15-19 and 23 are rejected, but the disclosure contains allowable subject matter. The following is the examiner's reason for indicating allowable subject matter. Applicants disclose an inhibitor ChePep-6 (the elected species) of human matrix metaloprotease MMP-9, which has potential clinical application in controlling wound healing, rheumatoid arthritis, osteoporosis, gastric ulcers and tumor metastasis.

As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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